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# Predicting Improvement in Gait After Stroke

## A Longitudinal Prospective Study

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Jos Twisk, PhD; Gert Kwakkel, PhD

**Background and Purpose**—To study the longitudinal relationship of functional change in walking ability and change in time-dependent covariates and to develop a multivariate regression model to predict longitudinal change of walking ability.

**Methods**—A total of 101 acute stroke patients with first-ever ischemic middle cerebral artery strokes was used as the population. Prospective cohort study based on 18 repeated measurements over time during the first poststroke year. Baseline characteristics as well as longitudinal information from functional ambulation categories (FAC), Fugl-Meyer leg score (FM-leg), Motricity index leg score (MI-leg), letter cancellation task (LCT), Fugl-Meyer balance (FM-balance), and timed balance test (TBT) were obtained. Intervention consisted of a basic rehabilitation program with additional arm, leg, or air splint therapy. Main outcome measure constituted change scores on FAC over time.

**Results**—In total, 1532 of the 1717 change scores were available for regression analysis. The regression model showed that TBT change scores were the most important factor in predicting improvement on FAC ( $\beta=0.094$ ;  $P<0.001$ ) followed by changes scores on FM-leg ( $\beta=0.014$ ;  $P<0.001$ ) and reduction in LCT omissions ( $\beta=-0.010$ ;  $P<0.001$ ) and MI leg test ( $\beta=0.001$ ;  $P<0.001$ ). In addition, time itself was significantly negatively associated with improvement ( $\beta=-0.002$ ;  $P<0.001$ ).

**Conclusion**—Improvement in standing balance control is more important than improvement in leg strength or synergism to achieve improvement in walking ability, whereas reduction in visuospatial inattention is independently related to improvement of gait. Finally, time itself is an independent covariate that is negatively associated with change on FAC, suggesting that most pronounced improvements occur earlier after stroke. (*Stroke*. 2005;36:2676-2680.)

**Key Words:** cerebrovascular accident ■ gait ■ longitudinal studies ■ prognosis ■ recovery of function

In the last 2 decades, there is growing interest in conducting longitudinal studies after stroke.<sup>1-4</sup> In these studies, the variables of interest are measured on the same individuals at several mostly fixed occasions. Findings from longitudinal studies with repeated measurements over time indicate that recovery of neurological impairments and disabilities show nonlinear recovery patterns over time.<sup>3-5</sup> According to Gresham, time itself appears to be one of the most important, although neglected, factors in our understanding of functional recovery after stroke.<sup>6</sup> To date, no study has been published that investigated the longitudinal time-dependent relationship between recovery of impairments, such as strength, synergism, visuospatial inattention, and recovery of disabilities such as gait after stroke. As a consequence, the impact of these changes as a function of time on regaining independent gait after stroke is not well understood. Moreover, knowledge about the relationship between specific impairments and limitations, such as balance control, would be useful in

selecting optimal treatment strategies for improving gait after stroke.

Within the last 2 decades, new statistical techniques such as random coefficient modeling (multilevel modeling or hierarchical modeling) have been developed that correct for the dependency of repeated measurements within each individual.<sup>7-9</sup> The use of this technique allows for analysis of the cross-sectional and longitudinal relationship between covariates simultaneously while taking the dependency of repeated measurements of individuals into account.<sup>9</sup> In standard multilevel hierarchical regression modeling, the regression coefficients presented collectively reflect the cross-sectional (ie, so-called between-subjects variation) as well as the longitudinal relationship (ie, so-called within-subject variation) between determinant(s) and outcome. This constitutes a limitation in the event the absolute differences between subjects exceed the changes over time. Consequently, the longitudinal within-subject relationships will be more or less overruled by

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the cross-sectional relationships.<sup>10</sup> This is likely to occur in particular when the time periods between repeated measurements are relatively short and the within-subject correlation high, which is often the case in stroke.<sup>4,11</sup> Because of this limitation, we elected to use a model in which the cross-sectional component is more or less “removed” from the analysis by modeling only change scores. By modeling longitudinal change scores, one can develop a rationale for the impact of improvements of underlying functions, such as strength, synergism, and balance control on changes in walking ability (ie, quasi-causal relationships).<sup>10</sup>

In the present study, we initially investigated the bivariate longitudinal relationship of improvements in walking ability and patient characteristics at baseline and improvements in impairments and functional limitations during the first year after stroke using the following time-dependent covariates: leg strength, leg synergism, visual hemi-inattention, and balance control. Subsequently, we developed a multivariate multilevel regression model for the prediction of functional improvements in gait as a function of time.

## Materials and Methods

### Design and Procedures

This prospective cohort study was part of a randomized clinical trial conducted to study the effects of intensity of rehabilitation on stroke outcome.<sup>4</sup> In this study, 101 stroke patients participated with a mean age of 65 years (SD 12.0). Patients were included when they met the following criteria: (1) they were between 30 and 80 years of age; (2) they experienced an ischemic, first-ever stroke involving the territory of the middle or anterior cerebral artery as revealed by computed tomography or MRI scan; (3) they displayed inability to walk at first assessment; (4) they revealed no complicating medical history such as cardiac, pulmonary, or orthopedic disorders; (5) they had no severe deficits in communication, (6) they had no severe deficits in memory and understanding, and (7) they had provided written or verbal informed consent and demonstrated sufficient motivation to participate. Details about design and outcome are published previously.<sup>4</sup>

### Measurements

To investigate the longitudinal impact of recovery from impairments on gait, we modeled first-order change scores from 18 repeated measurements of different impairments to fit the change scores observed in walking ability.<sup>4</sup> All time-dependent measurements were taken weekly, starting from within 14 days after stroke onset. From week 10 to week 20, biweekly measurements were obtained, whereas follow-up measurements were performed at 26, 38, and 52 weeks after stroke. All assessments were done by 1 observer (G.K.) who was blinded for treatment assignment. Walking ability was assessed with the functional ambulation categories (FAC). The FAC is a reliable and valid assessment comprising of 6 categories designed to provide information on the level of physical support needed by patients to ambulate. Walking devices were allowed to be used during the measurements with the exception of a rollator or walker. Age, gender, hemisphere of stroke, and social support were used as time-independent covariates and severity of paresis, stage of synergism, control for standing balance, and severity of visuospatial inattention as time-dependent covariates in the multilevel regression model.

Motricity index (MI) was used to measure strength in upper and lower extremities. This instrument reliably assesses the presence of a paresis in stroke patients. It uses a weighted score to a maximum of 100 points for each extremity and is derived from the Medical Research Council grades. It tests 6 limb movements. Balance was measured with the timed balance test (TBT). This instrument consists of 5 components on an ordinal scale and involves timed balance (ie, 60 seconds) on progressively diminishing support

surfaces. The Fugl-Meyer evaluation was used to assess motor performance. The motor section of this extensive test consists of upper limb, wrist, hand, as well as lower limb ordinal scaled components. Basically, it grades the degree to which dependence on synergic movements is present. Finally, the letter cancellation task (LCT) was applied to demonstrate the presence of neglect. Patients are requested to cross certain letters among many letters of the alphabet on a sheet of paper containing 5 lines of letters (34 per line). The difference in the number of crossed letters on the paretic and nonparetic side is scored.

### Statistical Analysis

The random coefficient analysis was performed with MLwiN.<sup>12</sup> The iterative generalized least-squares algorithm was used to estimate the regression coefficients.<sup>13</sup> Before conducting the random coefficient analysis, we calculated the change between subsequent measurements of the time-dependent covariates. These change scores were then plotted to check for compliance with model assumptions. Because time constitutes an independent covariate, random coefficient analysis enables longitudinal analysis of unequally spaced time points of measurement.

To investigate the possible longitudinal association between walking ability on FAC and covariates, initially bivariate longitudinal regression analysis was conducted with FAC change scores and time-independent covariates at baseline, such as age, gender, and lateralization of stroke, as well as with  $t-1$  change scores of the time-dependent covariates MI-leg, Fugl-Meyer leg score (FM-leg), Fugl-Meyer balance (FM-balance), TBT, and LCT (see Appendix, models 1 and 2). Subsequently, standardized regression coefficients were calculated, and a multivariate regression model for predicting functional recovery of gait based on FAC scores was developed (see Appendix, model 3).

The likelihood ratio test was used to evaluate the necessity for allowing random regression coefficients into the model, whereas the Wald test was used to obtain a  $P$  value for a particular regression coefficient.<sup>10</sup> For all tests, a 2-tailed significance level of 0.05 was used.

## Results

Patient characteristics of all 101 stroke patients are presented in Table 1. None of the stroke patients participating in our study were able to walk unassisted during the first week after stroke onset. Mean recovery profiles for MI leg, FM-leg, FM-balance, LCT, and TBT for all 18 measurements are illustrated in the Figure. In total, 1530 of the 1717 change scores were available for modeling. All change scores were normally distributed based on visual plotting.

### Bivariate Random Coefficient Analysis of Change Scores

Table 2 shows the bivariate regression coefficients, their errors, and significance for time-independent covariates and change scores of time-dependent covariates. Except for age ( $P=0.046$ ) none of the time-independent covariates was significantly associated with the change scores of FAC. However, all time-dependent covariates were statistically significantly associated with the change scores on FAC. The highest regression coefficient was observed for improvements on the TBT followed by the FM-balance, FM-leg, LCT, time, and MI-leg. Time after onset and LCT showed to be negatively associated with change on FAC.

### Multivariate Random Coefficient Modeling of Significant Time-Dependent Covariates

Table 3 presents the significant covariates of the multivariate random coefficient model. This model includes change scores

**TABLE 1. Patient Characteristics**

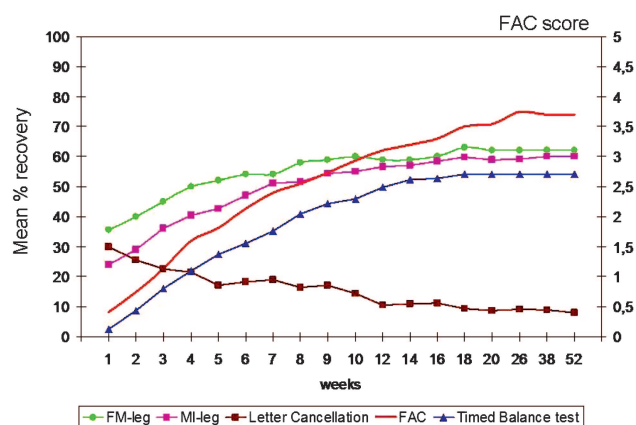
Group	Total
n	101
Gender (female/male)	43/58
Age, years ( $\pm$ SD)	65.4 (10.5)
MMSE ( $\pm$ SD)	26.4 (2.5)
Hemisphere of stroke (left/right)	41/61
Type of stroke (OCSP)	
TACI	55
PACI	33
LACI	14
OPS ( $\pm$ SD)	4.4 (0.8)
GCS ( $\pm$ SD)	14.8 (0.8)
Cognitive disturbances (%)	
Aphasia (0/1) <sup>†</sup>	27.5
Inattention (0/1)	49.0
Impairments of vision (%)	
Hemianopia (0/1)	31.4
Visual gaze deficit (0/1)	23.5
Days between stroke onset and first assessment ( $\pm$ SD)	7.3 (2.8)
MI-arm( $\pm$ SD)	13.5 (23.3)
MI-leg( $\pm$ SD)	21.7 (24.4)
Sitting balance (0/1)	26/76
BI (%) ( $\pm$ SD)	28.5 (17.2)
FAC score ( $\pm$ SD)	0.8 (1.0)
ARA score ( $\pm$ SD)	3.9 (9.7)
Risk factors (%)	
Hypertension (160/95) (0/1)	45.1
Smoking habit (0/1)	36.3
Family hereditary (0/1)	31.3
Cardiac disease (0/1)	28.4
Diabetes mellitus (0/1)	14.7
hyperlipidemia (0/1)	9.8

n indicates number of patients; SD in brackets; (0/1), no/yes; MMSE, mini-mental state examination (range 0–30); OCSP, Oxford Community Stroke Project; TACI, total anterior circulation infarcts; PACI, partial anterior circulation infarcts; LACI, lacunar anterior circulation infarcts; OPS, Orpington prognostic score (range 1.6–6.8); GCS, Glasgow coma scale (range 0–15). MI, motricity index, range 0–200; BI indicates Barthel index (range 0–100); FAC, functional ambulation categories, range 0–5; ARA, action research arm test (range 0–57). <sup>†</sup>Based on the Dutch Foundation Aphasia test (ie, SAN).

of the covariates TBT, FM-leg, LCT, MI leg, as well as time itself. This model predicted 18% of the variance of outcome on change of FAC.

## Discussion

To the best of our knowledge, this is the first longitudinal study that investigated the functional impact of observed changes of time-dependent covariates such as balance,<sup>14</sup> synergism,<sup>15</sup> leg strength,<sup>16</sup> visuospatial inattention,<sup>17,18</sup> and time<sup>3</sup> on the recovery of gait after acute stroke. The significant bivariate random coefficients found in the present study confirm the assumption that larger improvements in impairments and gait-related functional limitations, including con-



Mean normalized recovery patterns (percentage of maximum attainable recovery) for impairments as a function of time (n=101; left y axis). Mean recovery patterns (raw change scores) for FAC (right y axis). FM-leg indicates Fugl-Meyer leg; MI-leg, motricity index leg.

trol of standing balance, are highly associated with improvements in gait. The present study further shows that improvement in standing balance, as measured with the TBT test or FM-balance test, is the most important determinant for regaining gait based on the FAC, whereas changes in synergism and muscle strength of the paretic leg are less associated with recovery of walking ability. This finding is in agreement with the literature suggesting that recovery in postural control of standing is more important for regaining gait than the restoration of support functions and voluntary control of the paretic leg itself. This finding also suggests that the use of compensatory strategies in the standing position (eg, shifting the weight to the nonparetic side) is more important than muscle strength in the lower paretic limb for regaining gait.<sup>14,19,20</sup>

Interestingly, the present findings also show that visuospatial inattention was weakly but significantly and negatively related to recovery of gait, suggesting that more reductions in visuospatial inattention, as expressed by the difference in the number of omissions in the LCT, are associated with better improvements in gait. This latter finding is in agreement with the studies that show that patients with visuospatial neglect experience more difficulty in negotiating obstacles<sup>21</sup> and walking appropriate trajectories than controls.<sup>18</sup>

Finally, time itself is an independent fixed determinant in the multivariate model that is significantly negatively associated with recovery of gait, suggesting that most improvements take place sooner after stroke. This finding is in agreement with the general assumption about the speed of neurological (and with that, functional) recovery after stroke (ie, the largest improvements are observed early after stroke onset and these changes subsequently gradually level off).<sup>3,6,22</sup> However, in part, gradual smaller change scores over time may have been the result of the availability of a reduced range for changes (ceiling effect).

The major advantage of a repeated measurement design compared with a traditional prognostic design is that it represents reality far better than just 2 measurements over time. Instead of observing 2 images of the patients' functional



**TABLE 2. Bivariate Regression Coefficients With Random and Fixed Slopes (standard errors (SEs) in parenthesis) for Time-Independent and Time-Dependent Covariates for Recovery of Gait During the First Year After Stroke**

	n=101		
Determinant	$\beta$ Value ( $\beta$ -error)	P Value	
Time-independent covariates	Fixed Slope		
Gender (male/female)	0.010 (0.025)	0.69	
Age (range 30–80 years)	−0.002 (0.001)	0.05*	
Hemisphere of stroke (left/right)	−0.006 (0.025)	0.81	
Type of stroke (OCSF)	−0.023 (0.020)	0.25	
Days between stroke onset and first assessment	−0.002 (0.004)	0.62	
MMSE	0.008 (0.005)	0.11	
Visual gaze deficit (0/1)	−0.011 (0.029)	0.70	
Homonymous hemianopia (0/1)	−0.018 (0.027)	0.51	
Baseline visual inattention (0/1)	−0.027 (0.025)	0.28	
Baseline TFT score (0–3)	−0.014 (0.013)	0.28	
Baseline OPS (1.6–6.8)	0.013 (0.013)	0.32	
Baseline sitting balance (0/1)	0.050 (0.028)	0.07	
Urinary incontinence (0/1)	−0.013 (0.025)	0.60	
Baseline MI-leg	0.000 (0.000)	—	
Baseline FM-leg	0.001 (0.002)	0.62	
Baseline TCT	0.001 (0.000)	0.32	
Baseline FM-balance	0.008 (0.005)	0.11	
Baseline TBT	0.007 (0.015)	0.64	
Baseline FAC	0.007 (0.013)	0.59	
Baseline Barthel index	0.004 (0.003)	0.18	
Social support (0/1)	−0.021 (0.026)	0.42	
Time-dependent Covariates	Fixed Slope	Random Slope	
$\Delta$ MI leg	...	0.014 (0.002)	0.00***
$\Delta$ FM-leg	0.053 (0.005)	...	0.00***
$\Delta$ FM-balance	...	0.091 (0.015)	0.00***
$\Delta$ LCT	...	−0.025 (0.007)	0.00***
$\Delta$ TBT	0.116 (0.019)	...	0.00***
Time of measurement after stroke	−0.018 (0.003)	...	0.00***

(0/1) indicates no/yes;  $\Delta$ , change score of 1 time lag (ie, from t to t−1); n, No. of patients;  $\beta$  value, regression coefficient; OCSF, Oxford Community Stroke Project; MMSE, mini-mental state examination (range 23–30); TFT, thumb finding test (range 0–3); OPS, Orpington prognostic score (range 1.6–6.8); LCT, letter cancellation task; TBT range 1–5; MI-leg range 0–100; FM-leg total score range 0–34; FM-balance total score range 0–34. \* $P<0.05$ ; \*\* $P<0.01$ ; \*\*\* $P<0.001$ .

status frozen in time, it becomes feasible to analyze several closely sequential images over time, providing insight into the dynamics of recovery. This, in turn, allows for a more valid interpretation of the factors that modulate the process of spontaneous neurological recovery.

More research is needed for the development of prognostic models based on the within-subject variability of covariates as a function of time for the accuracy of functional change.

**TABLE 3. Multivariate Regression Model for Progress of Walking Ability During the First Year After Stroke**

Fixed Effect	n=101		
	Standardized $\beta$ Coefficient	SE	P Value
Intercept	0.215	0.029	<0.00***
$\Delta$ TBT	0.094	0.019	0.00**
$\Delta$ FM-leg	0.014	0.005	<0.00***
$\Delta$ LCT	−0.010	0.006	0.00**
Time	−0.002	0.003	0.01**
$\Delta$ MI-leg	0.001	0.002	<0.00***

$\Delta$  indicates change score of 1 time lag (ie, from t to t−1); n, No. of patients;  $\beta$  value, regression coefficient. \* $P<0.05$ ; \*\* $P<0.01$ ; \*\*\* $P<0.001$ . FM-leg total score range 0–34; LCT, letter cancellation task range 0–20; TBT, timed balance test.

To understand the impact of time after stroke on recovery, future research should focus on the impact of individual neurological changes of impairments on functional recovery and the significance of using compensatory strategies to improve gait.<sup>3,14,20,23</sup> This information can then be used to determine the relationship between recovery of impairments and disabilities, such as gait.<sup>3</sup> Recovery of disabilities reflects the intrinsic recovery of impairments as well as applied compensation.<sup>3</sup> Understanding the different mechanisms involved as well as the optimal time windows for functional recovery allows clinicians to develop treatment programs that are more effective in maximizing underlying mechanisms responsible for neurological and adaptive (ie, compensatory) recovery.<sup>3,5,24</sup>

The relatively low regression coefficients observed for the covariates and the low explained variance of  $\approx 18\%$  for included determinants suggest that most progress cannot be explained by restitution of function. Most likely this progress is facilitated by the use of compensation strategies that involve the participation and adaptation of the nonparetic side to enable gait. This latter finding suggests that recovery after stroke occurs to a large extent through behavioral compensation rather than via processes of “true recovery” alone.<sup>5</sup> Future studies may explore the relationship between observed behavioral adaptations and improved skills after stroke by addressing the issue of which changes in motor control coincide with functional improvements. This knowledge may contribute to determining the best way to subject stroke patients to therapeutic exercises.

Finally, modeling change scores in a repeated measurement design (whereby the measures are nested within the subjects) offers also opportunities for the exploration of the longitudinal relationship between, on the one hand, macroscopic neuroplastic changes observed (eg, functional MRI and TMS), and, on the other hand, found changes in neurological and kinematical examination.

## Appendix

For the bivariate longitudinal regression analysis of time-dependent variables, we used the following regression model:  $(Y_{it} - Y_{it-1}) = \beta_{0it} + \sum \beta_{ij} (X_{ijt} - X_{ijt-1}) + \epsilon_{it}$  (model 1), where  $Y_{it}$  are the observations for subject I at time t and  $Y_{it-1}$  the observations for subject I at time t−1, reflecting the change score for the dependent variable “walking

ability” based on FAC registration. Regression coefficient  $\beta_{0it}$  reflects the random intercept and  $\beta_{1j}$  the random selected regression coefficient for the time-dependent covariate  $j$  and  $X_{ijt}$  the time-dependent variable  $j$  for subject  $I$  at time  $t$  and  $X_{ijt-1}$  at time  $t-1$ .

For the bivariate longitudinal regression analysis of time-independent variables, we used the following model:  $(Y_{it} - Y_{it-1}) = \beta_{0it} + \sum \beta_{1m} X_{im} + \epsilon_{it}$  (model 2), where  $Y_{it}$  are the observations for subject  $I$  at time  $t$  and  $Y_{it-1}$  the observations for subject  $I$  at time  $t-1$ , reflecting the change score for the dependent variable “walking ability” measured with the FAC. Regression coefficient  $\beta_{0it}$  is a random intercept and  $\beta_{1m}$  the regression coefficient of the time-independent covariate  $m$  and  $X_{im}$  the time-independent covariate for subject  $I$ .  $\epsilon_{it}$  represents the error for subject  $I$  at time  $t$ .

To develop a multivariate regression model for predicting functional recovery of gait based on FAC scores, the following statistical model was used:  $(Y_{it} - Y_{it-1}) = \beta_{0it} + \sum \beta_{1j} (X_{ijt} - X_{ijt-1}) + \beta_2 t + \sum \beta_{3m} X_{im} + \epsilon_{it}$  (model 3), where  $Y_{it}$  are the observations for subject  $I$  at time  $t$  and  $Y_{it-1}$  the observations for subject  $I$  at time  $t-1$ , reflecting the change scores for the dependent variable “walking ability” measured with the FAC. Regression coefficient  $\beta_{0it}$  is a random intercept and  $\beta_{1j}$  the random selected regression coefficient for time-dependent variable  $j$  and  $X_{ijt}$  the time-dependent variable  $j$  for subject  $I$  at time  $t$  and  $X_{ijt-1}$  at time  $t-1$ .  $\beta_2$  is the regression coefficient for time  $t$  and  $\beta_{3m}$  the regression coefficient for time-independent covariate  $m$  and  $X_{im}$  the time-independent covariate. Finally,  $\epsilon_{it}$  represents the error for subject  $I$  at time  $t$ .

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